

Product R&D for neglected diseases

Twenty-seven years of WHO/TDR experience with public–private partnerships

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The Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975 by the United Nations' Development Programme, the World Bank and the World Health Organization (WHO), at a time when only minimal scientific worldwide effort was dedicated to research into tropical diseases (Morel, 2000). TDR was therefore created with a core mission of fighting these diseases and has two specific goals: first, it seeks to identify and develop new tools and methods to control tropical diseases; and second, it seeks to develop research capacities in developing countries so that their investigators are able to establish their own research activities and contribute to the control of diseases that affect their countries.

Because of its mission, TDR has always been involved in product research and development (R&D) activities and has achieved some notable successes in chemotherapy. In performing its work, it has, from the outset, recognized the need for and value of collaborating with the pharmaceutical industry. A retrospective analysis of new drugs that were approved between 1972 and 1997 illustrates the value of this approach (Pecoul *et al.*, 1999; Trouiller *et al.*, 2001). Of 1,450 new chemicals introduced to the global market, only 13 were specifically for treating neglected infectious diseases, and many of these substances came out of R&D for other

disease indications, such as veterinary medicine and cancer. Through its work with industry, TDR was crucially involved in the development of about half of these new drugs. In this article, I highlight how TDR has worked effectively with industry over the past 27 years, identify several key achievements and indicate how future activities might develop in this area.

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TDR consists of four main functional areas: strategic research, product R&D, research related to the implementation of health strategies, and strengthening of research capacities. It is important to recognize that product R&D is not viewed as an isolated activity, but can receive input, ideas and projects from basic and strategic research and can also feed its registered products into more applied field testing and evaluation (Remme *et al.*, 2002; Fig. 1). The goal of TDR's product R&D activity is to register new products in a manner that permits their continued and sustainable availability and use in the target populations, which are most often

the poor and marginalized. This process starts with the characterization and profiling of the products required, which is greatly helped by TDR's physical location in WHO, where there is a high level of disease-specific expertise. This first step is followed by establishing competent drug development partnerships that can respond to these profiled needs. Table 1 outlines how TDR has responded to some of these challenges in the past and describes some of its continuing drug development activities.

For malaria, from which most deaths occur in sub-Saharan Africa, there is an urgent need for new drugs that both overcome resistance and are safe and effective for use in young children and pregnant women (Ridley, 2002). In response to this need, TDR has partnered the development of a new antimalarial, Lapdap, with Glaxo SmithKline (Winstanley, 2001; Lang & Greenwood, 2003) and instigated the creation of the Medicines for Malaria Venture (MMV; Ridley, 2000). Together with MMV, TDR is now actively developing several fixed-dose artemisinin combinations, notably Lapdap plus artesunate and also pyronaridine plus artesunate, each with a pharmaceutical company partner.

The drugs that have been historically available to treat visceral leishmaniasis, which affects over 500,000 people worldwide (Figs 2,3), have been injectables that are administered in a hospital setting over 28 days. This puts a tremendous strain on resource-poor infrastructures. Furthermore, parasites are now developing resistance to the established drugs. Recently TDR, in partnership with Zentaris, a small German pharmaceutical company, has developed a new oral drug, miltefosine (Sundar *et al.*, 2002). Phase 4 studies are currently in progress in cooperation with Indian control authorities and the Indian Council for Medical Research to assess miltefosine's potential more fully. TDR is also about to start phase 3 studies with another new drug against this disease, paromomycin, in partnership with the Institute of One World Health.

Strengthening research capacity

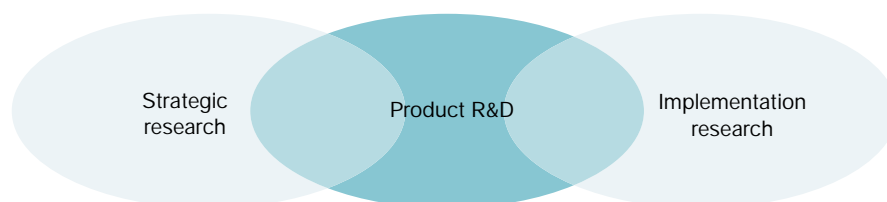


Fig. 1 | Simplified structure of the Special Programme for Research and Training in Tropical Diseases (TDR), showing that product research and development (R&D) activities are linked to both 'upstream' basic and strategic research and to 'downstream' applied fieldwork through implementation-related research. All these activities operate within an infrastructure that promotes and emphasizes the building of research capacity.

Table 1 | The Special Programme for Research and Training in Tropical Diseases (TDR)'s drug development for tropical diseases: summary of important drug registration successes and examples of some current activities

Disease	Problems with existing drugs	TDR response	Partner	Current status
Uncomplicated malaria	Resistance	Lapdap	Glaxo SmithKline	Dossier submitted (2002)
	Long treatment regimes (artemisinins)	Lapdap/artesunate	Glaxo SmithKline	Phase 1
		Pyronaridine/artesunate	Shin Poong	Preclinical
Severe malaria	Slow acting	Intramuscular arteether	Artecef	Registered (2000)
	Require hospitalization	Rectal artesunate	Under discussion	FDA approvability letter received
Visceral leishmaniasis	Injectable	Miltefosine	Zentaris	Registered (2002) and phase 4 studies initiated
	Resistance	Paromomycin	Institute of One World Health	Phase 3 studies about to be started
African sleeping sickness	Injectable	Intravenous eflornithine	Aventis	Registered (1991)
	Toxic			Made available (in part by donation)
River blindness	Lack of treatment	Ivermectin	Merck	Registered (1989)
				Made available by donation Successful control programme

FDA, US Food and Drug Administration.

For African trypanosomiasis (Fig. 4; commonly known as sleeping sickness and caused by *Trypanosoma brucei*), the problem is, if anything, even more acute. We are still relying on old drugs, such as suramin, a relic of the 1920s, and melarsoprol, registered back in 1949. The latter is highly toxic, and is perhaps the only arsenical drug still in clinical use. All current treatments have the disadvantage that they are injectable. The most recent addition to the arsenal against African trypanosomiasis came in 1991, with the registration of an intravenous formulation of eflornithine. This drug was developed by TDR in collaboration with Marion Merrell Dow, now Aventis, and is highly effective against the disease in its later stages (Fig. 5). It has had a significant impact and has been dubbed the 'resurrection drug'

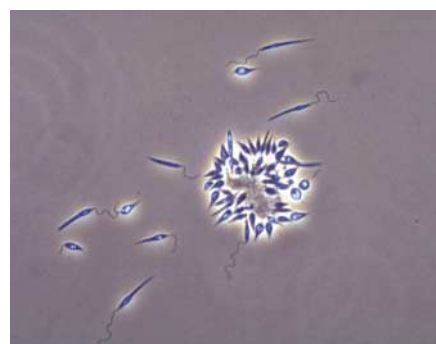


Fig. 2 | *Leishmania donovani* in the promastigote stage (© (2000) WHO/TDR Sinclair Stammers).

In the 1980s, TDR-sponsored scientists found that ivermectin, a veterinary product, might be effective for the treatment of onchocerciasis

because of its ability to bring people back from the brink of death. However, it is not a magic bullet against sleeping sickness. The drug is expensive, and is only active against one of the species that causes human African trypanosomiasis (*T. b. gambiense*) and not the other (*T. b. rhodesiense*), which has limited its use. The highly toxic melarsoprol is still sometimes the only recourse left to physicians to treat the late stage of the disease.

For onchocerciasis (river blindness; Fig. 6) the situation is currently stable. This was not true 20 years ago, when the only drug available for its treatment was diethyl carbamazine, a drug that often produced severe pathological side-effects. In the 1980s, TDR-sponsored scientists found that ivermectin, a veterinary product, might be effective for the treatment of onchocerciasis. TDR worked with Merck to develop the product, which was registered in 1989. After that, Merck made a commitment to make the drug available, free of charge, for as long as it is needed to treat the disease. This commitment allowed the creation of a major control programme for onchocerciasis that has since been funded by numerous

governments and other agencies (Fig. 7). As a result, what used to be a barrier to socio-economic development has been almost eliminated in a relatively short space of time. More than 40 million people are now protected from onchocerciasis. More than 12 million children born after 1974 have grown up without the risk of the disease and the resulting blindness. Over 25 million hectares of fertile river-side land have been made available for resettlement, and the additional agricultural production is sufficient to feed 17 million people. However, despite these successes there is still a need for improved drugs. Ivermectin kills only the microfilariae that cause the pathology of 'river blindness', not the adult worms that can reside in the body for many years. Consequently, the control programme is based on a single annual presumptive treatment to prevent the growth of microfilariae. If we had a macrofilaricide that killed the adult worms it would be possible to cure individuals of the disease, and possibly eliminate the need for annual treatment. Obtaining such a drug is the main goal of TDR's current research activities in this area.

The building of local expertise and knowledge of a particular drug through drug development activities has major benefits for the later implementation of new drugs

As well as developing new treatments for neglected tropical diseases, how this work is undertaken is just as important to TDR. As mentioned above, its mission is also to build research capabilities in developing countries. TDR therefore takes great pains to ensure that scientists in developing countries are closely involved in their drug development projects. The output from this approach can sometimes be remarkable, not only in terms of the careers of capable scientists, but also in helping in the firm establishment of research institutions.

TDR's drug development activities have helped to strengthen capabilities particularly in the area of clinical research. Because the vast majority of TDR's clinical studies take place in developing countries, the local clinical researchers can readily participate in and manage them. Each study requires extensive preparation for and training in the art of conducting clinical studies and writing protocols. During the past several years, a network of clinical researchers that are trained in good clinical practice has been developed, together with a network of clinical trial monitors. Many of the clinical studies undertaken in partnership with Zentaris took place in the Indian state of Bihar, where 90% of visceral leishmaniasis in India occurs. All the clinical investigators involved in these studies came from Bihar. After discussions with the Indian Council



Fig. 3 | A cutaneous leishmaniasis lesion in a young Iranian boy (© (1996) WHO/TDR Andy Crump).



Fig. 4 | Head and biting mouth-parts of a tsetse fly that spreads the trypanosomiasis parasite (© (1991) WHO/TDR Douglas Fisher).

of Medical Research, it was decided to involve the Rajendra Memorial Institute of Medical Sciences in Patna as well. The impact of these studies on the Institute and the Institute's development has been remarkable (Bhattacharya, 2002), and it is now becoming increasingly recognized as a centre of excellence for undertaking clinical studies.

The building of local expertise on and knowledge of a particular drug through drug development activities has major benefits for the later implementation of new drugs. The value of local ownership has been amply demonstrated in the case of onchocerciasis control, through the Onchocerciasis Control Programme and the African Programme for Onchocerciasis Control, both based in West Africa. More recently we have seen this again in the development of miltefosine. Indian investigators, linked to the Indian Council for Medical Research, were heavily involved in all clinical development activities. This in turn meant that the national control authorities and the Ministry of Health were continuously kept abreast of developments and any practical issues. Once the drug had been registered, the Indian authorities were therefore in a position to implement phase 4 studies efficiently to assess how the drug would behave in real-life situations and whether it could be introduced into national policy. More than 1,200 patients are being enrolled in these studies, which are taking place in Bihar, India, and in neighbouring countries that are affected by visceral leishmaniasis, including Bhutan, Nepal and Bangladesh.

TDR is also paving the way for other compounds that are under development at present to be rapidly tested and

evaluated in appropriate phase 4 studies after their registration. The two compounds most advanced in this respect are rectal artesunate, which has recently received a letter of approvability from the US Food and Drug Administration, and Lapdap, for which a dossier has recently been submitted to the UK's Medicines Control Agency. For rectal artesunate, phase 4 studies are now being implemented to assess its potential value; for Lapdap, several studies are planned, subject to regulatory approval (Winstanley, 2001; Lang & Greenwood, 2003).

As we move into the twenty-first century we hope that more organizations will develop an interest in the need to discover and develop new drugs for the diseases of the poor

All these cases highlight the value of performing drug development as a public-private partnership involving both industry and international organizations. If a product is developed solely by industry it can be several years after its registration before it finds its way into public health use. The reason for this delay is the need of the public sector to gain an understanding of the product and, quite often, to develop a relationship with the commercial company to ensure appropriate public-health-directed phase 4 studies. If the public sector has partnered the product through development, an easier transition to appropriate phase 4 studies can be made, and a more efficient decision-making process can be put in place to assess its future role in public health.



Fig. 5 | A male patient in the final stages of African sleeping sickness (trypanosomiasis) (© (1990) WHO/TDR).

Many good things are now starting to happen in the area of neglected diseases. In addition to enhanced bilateral government support for disease control, the Global Fund to Fight AIDS, Tuberculosis and Malaria (www.globalfundatm.org) has been established. It is starting to disburse funds to countries that will allow them to develop and implement meaningful control strategies for these diseases, including the purchase of much-needed drugs. TDR is also being joined in the area of drug research and development for tropical diseases by new organizations. The MMV (www.mmv.org) and the Global Alliance for TB Drug Development (www.tb-alliance.org) were established in 1999 and 2000, respectively, and provide further public-private partnership mechanisms through which enhanced drug discovery and development activities can take place. New drugs, which supplement those in the TDR pipeline, are starting to be developed by these organizations. Nevertheless, there remains a continued need to build and maintain these operations so that they can fulfil their promise. There also remains a need to build and maintain similar activities for other diseases, such as African trypanosomiasis,



Fig. 6 | An old Nigerian man blinded by onchocerciasis. He is still able to make ropes and so earns some income to help support his family (© (1998) WHO/TDR Andy Crump).

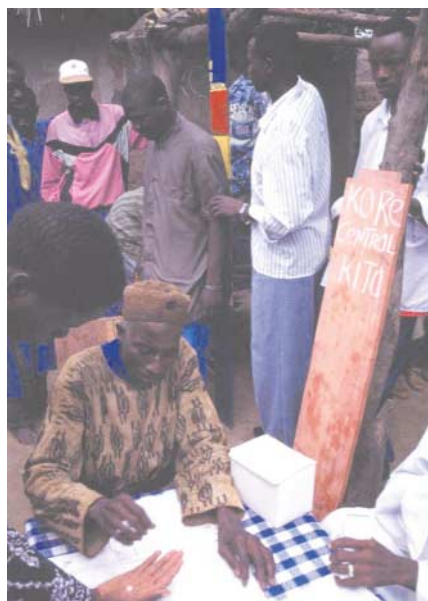


Fig. 7 | Distribution of ivermectin in Kita, Mali. The whole community gathers to receive their tablets. Records are made of everyone treated and of those who are absent so they can be treated later (© (1996) WHO/TDR Andy Crump).

schistosomiasis and leishmaniasis. In this regard, it is worth mentioning the Drugs for Neglected Diseases Initiative led by Médecins Sans Frontières (www.accessmed-msf.org), which seeks to bring additional resources to drug R&D for tropical diseases.

The past 27 years have been a difficult period for R&D into new drugs for tropical diseases. WHO/TDR, however, has managed to make an impact through its ability to partner pharmaceutical companies and its ability to assist in the development of new drugs. As we move into the twenty-first century, we hope that more organizations will develop an interest in the need to discover and develop new drugs for the diseases of the poor. It is also hoped that they will allow the fruits of academic scientific investigation to be translated effectively into new drugs and that the drugs will be accessible to the populations most

affected by these diseases. WHO/TDR, for its part, will continue to partner and assist all who wish to contribute to this crucial area of research and development to improve world health.

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